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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **MOLECULES HAVING IMMUNOMODULATORY ACTIVITY**

(57) Abstract: We describe an Fve polypeptide being a fragment, homologue, variant or derivative of Fve protein, which comprises at least one biological activity of Fve protein. Uses of such a polypeptide, etc, and nucleic acids encoding these, in the treatment and prevention of allergy and cancer are also disclosed.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/SG2004/000098

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 C12N15/29 A61K39/12 A61K39/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KO JIUNN-LIANG ET AL: "A new fungal immunomodulatory protein, FIP-fve isolated from the edible mushroom, Flammulina velutipes and its complete amino acid sequence" EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 228, no. 2, 1995, pages 244-249, XP008036978 ISSN: 0014-2956	1-7, 16, 17, 25-27, 31, 32, 35, 36
Y	see the whole document; especially p. 248, right col. last para.	8-15, 18-24, 28-30, 37-48, 77-79
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

10 February 2005

Date of mailing of the international search report

29. 04. 05

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/SG2004/000098

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KO JIUNN-LIANG ET AL: "Molecular cloning and expression of a fungal immunomodulatory protein, FIP-fve, from <i>Flammulina velutipes</i> " JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION, vol. 96, no. 7, 1997, pages 517-524, XP008036979 ISSN: 0929-6646	1-7,16, 17, 25-27, 31,32, 35,36
Y	see the whole document	8-15, 18-24, 28-30, 37-48, 77-79
A	----- HSU HAO-CHI ET AL: "Fip-vvo, a new fungal immunomodulatory protein isolated from <i>Volvariella volvacea</i> " BIOCHEMICAL JOURNAL, vol. 323, no. 2, 1997, pages 557-565, XP002300842 ISSN: 0264-6021	
A	----- MURASUGI A ET AL: "MOLECULAR CLONING OF A COMPLEMENTARY DNA AND A GENE ENCODING AN IMMUNOMODULATORY PROTEIN LING ZHI-8 FROM A FUNGUS <i>GANODERMA-LUCIDUM</i> " JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 4, 1991, pages 2486-2493, XP002300843 ISSN: 0021-9258	
P,X	----- PAAVENTHAN P ET AL: "A 1.7A Structure of Fve, a Member of the New Fungal Immunomodulatory Protein Family" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 332, no. 2, 12 September 2003 (2003-09-12), pages 461-470, XP004450110 ISSN: 0022-2836 see the whole document	54-58
Y	----- WO 99/06544 A (IMMUNE RESPONSE CORP INC) 11 February 1999 (1999-02-11) see the whole document, especially claims	8-15, 18-24, 28-30, 37-40
Y	----- US 5 917 026 A (LYCKE NILS ET AL) 29 June 1999 (1999-06-29) see especially col. 6, l. 13-50 ----- -/--	8,18

INTERNATIONAL SEARCH REPORT

International Application No
PCT/SG2004/000098

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/32866 A (HARE PETER FRANCIS JOSEPH O ; MARIE CURIE CANCER CARE (GB); ELLIOTT GI) 30 July 1998 (1998-07-30) see p. 18-21 -----	12, 20
A	WO 02/22680 A (WUEEST THOMAS ; PFIZENMAIER KLAUS (DE); WAJANT HARALD (DE); MOOSMAYER) 21 March 2002 (2002-03-21) -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2004/000098

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 53, 60-62, 80
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 31-48, 62, 65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 53, 60-62, 80
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1-48, 54-59, 63-67, 77-78
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7 (complete), 16,17, 25-26, 30,80 (all partially)

Fve polypeptides comprising at least one biological activity of native Fve protein, nucleic acids encoding said proteins, vectors and host cells comprising the nucleic acids, and pharmaceutical compositions comprising said proteins and nucleic acids

2. claims: 8-11,18-19 (complete),24-26, 30, 80 (all partially)

A fusion protein comprising a first portion of a Fve polypeptide comprising at least one biological activity of native Fve protein and a second portion comprising at least a fragment of an allergen, nucleic acids encoding said proteins, vectors and host cells comprising the nucleic acids, and pharmaceutical compositions comprising said proteins and nucleic acids

3. claims: 12,13,20,21,77,78 (complete), 24-26, 30, 80(partially)

A fusion protein comprising a first portion of a Fve polypeptide comprising at least one biological activity of native Fve protein and a second portion comprising at least a fragment of a viral antigen, nucleic acids encoding said proteins, vectors and host cells comprising the nucleic acids, and pharmaceutical compositions comprising said proteins and nucleic acids

4. claims: 14,15,22,23 (complete), 24-26, 30, 80 (partially)

A fusion protein comprising a first portion of a Fve polypeptide comprising at least one biological activity of native Fve protein and a second portion comprising at least a fragment of a tumor-associated antigen, nucleic acids encoding said proteins, vectors and host cells comprising the nucleic acids, and pharmaceutical compositions comprising said proteins and nucleic acids, and the use of said proteins or nucleic acids for medical treatment, for identifying molecules capable of binding the protein or for amplifying a sub-population of cells

5. claims: 31-32

Use of a Fve polypeptide as an immunomodulator or to enhance the immune response in a mammal

6. claims: 33, 63-67

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a Fve polypeptide to stimulate proliferation of CD3+
CD8+ CD18+ bright T cells and amplified cells obtained by
said methods

7. claim: 34

Use of a Fve polypeptide to stimulate proliferation of CD3+
CD16+ CD56+ natural killer T cells

8. claims: 35-36

Use of a Fve polypeptide to stimulate production of IL-2,
IL-10, TGF-beta, IFN-gamma or TNF-alpha in CD3+ cells

9. claim: 37

Use of a Fve polypeptide as an adjuvant for a vaccine

10. claims: 38-45

Use of a Fve polypeptide in the treatment of a disease

11. claims: 49-53

A method for identifying a molecule capable of binding to
Fve and molecules identified by said method

12. claims: 54-59

A native Fve polypeptide in crystalline form and a model
making use of the crystal

13. claims: 68-75, 79

A combination comprising a first component comprising an
immunomodulator and a second component comprising at least a
fragment of an allergen, a viral antigen or a tumor
associated antigen

14. claim: 76

An immunomodulator-antigen conjugate

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box II.1

Although claims 31-48,62,65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 53,60-62,80

The "molecule" according to Claim 52 is exclusively characterised by its method of isolation, i.e. by a capability to "bind" Fve. Besides the fact that the expression "binding" is totally vague, the lack of true technical features in order to characterise the claimed molecule renders a meaningful search for said claim (and consequently also for claims 60-62) impossible.

A search was neither possible with regard to Claim 80 since neither the category nor the scope of said claim is clearly defined.

Finally it should be mentioned that also with regard to Claims 5 and 6 belonging to the first group which has been searched, a complete search was impossible since, due to the totally broad scope (which is only limited by the short sequence motif), an initial sequence search revealed an overflow of relevant documents (see also non-unity motivation).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/SG2004/000098

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9906544	A	11-02-1999	US 5891432 A	06-04-1999
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